PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003362	14.10.2004	15.10.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/496, C07D207/408, C07D207/416, A61P13/08, C07D209/48

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/003362

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 39-48(with respect to industrial applicability)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 39-48

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-5,8-9,12-57
	No:	Claims	1, 6-7,10-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-57
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 39-48 relate to subject-matter considered by this Authority to be covered by the provision of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims(article 34(4)(a)(i)PCT).

The present Claims 1, 49-57 do not meet the requirements of Article 6 PCT in that the matter for which the protection is sought is not clearly defined. The functional terms "prodrug" and "metabolites" do not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of the said claims. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful examination impossible.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Reference is made to the following documents:**

D1: WO 02/44151 A (ANAND NITYA ; CHUGH ANITA (IN); JAIN SANJAY (IN); SINHA NEELIMA (IN);) 6 June 2002 (2002-06-06)

D2: PALUCHOWSKA, MARIA H. ET AL: "On the Bioactive Conformation of NAN-190 (1) and MP3022 (2), 5-HT1A Receptor Antagonists" JOURNAL OF MEDICINAL CHEMISTRY , 42(24), 4952-4960 CODEN: JMCMAR; ISSN: 0022-2623, 1999, XP002314916

D3: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; "Succinimide derivatives" XP002314917 retrieved from STN Database accession no. 1985:615155

D4: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; "Cyclic imide derivatives" XP002314918 retrieved from STN Database accession no. 1984:591971

D5: WO 01/05765 A (RECORDATI CHEM PHARM ; RECORDATI CHEM PHARM (IT)) 25 January 2001 (2001-01-25)

D6: WO 00/05206 A (SAXENA ANIL KUMAR ; ANAND NITYA (IN); JAIN SANJAY (IN); MEHTA ANITA (I) 3 February 2000 (2000-02-03)

D7: HIEBLE J P ET AL: "RECENT ADVANCES IN THE IDENTIFICATION OF ALPHA1- AND ALPHA2-ADRENOCEPTOR SUBTYPES: THERAPEUTIC IMPLICATIONS" EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 6, no. 4, April 1997 (1997-04), pages 367-387, XP000981272 ISSN: 1354-3784

2. **Novelty** (Article 33(1) and 33(2)PCT)

The present application discloses compounds of formula (I) (see present Claim 1) as adrenergic receptor antagonists.

The compounds 1, 8, 11, 18, 23-25 disclosed by D1 in pages 8-10 represent novelty destroying compounds for the present claimed formula (I). Moreover, the present Compound 113, claimed by the present Claim 36(page 76) it was already disclosed by D1 as compound 18 (page 9).

D2 (compound 8 table 1-page 4954), D3(compound with rn:99012-73-4P) and D4(compound with rn: 92636-57-2P) disclose compounds which are novelty destroying embodiments for the subject-matter of the present Claim 1.

Consequently, considering the fact that the documents D1-D4 disclose compounds having structures which fall under general formula I of the present case, the present application does not meet the requirements of Article 33(1) and (2) PCT.

4. **Inventive step** (Article 33(1) and 33(3) PCT).

Since, D1-D4 disclose novelty destroying embodiments for the general structure claimed by the present Claim 1, an inventive step can be discussed only for the novel compounds of the present application (e.g. the compounds claimed by Claim 2,3, 12-33).

The present claimed compounds are 1-(1-alkylpiperazinyl)-pyrrolidin-2,5-diones which may be substituted in positions 3 or 4 of the pyrrolidine ring with an alkyl, cycloalkyl or R3R4-N(CH2)m- moiety or may have the pyrrolidine ring condensed

with a cyloalkyl or cycloalkenyl ring. The present compounds are adrenergic receptor antagonists and are useful thereof to treat benign prostatic hyperplasia as well as lower urinary tract symptoms.

D1, which is regarding as being the closest prior art, disclose 1-(1-alkylpiperazinyl)-tetrahydroisoindole derivatives as alpha-1-adrenergic receptor blockers. The D1 compounds present the same structure as the present case when R1 and R2 form together a cycloalkenyl ring(some of the D1 compounds are novelty destroying embodiments for the present formula (I)).

D6 disclose compounds (see compounds 2-page 7 and compound 26-page 8) which differ only through the nature of the R1 substituent which is a direct phenyl ring linked on the pyrrolidin-2,5-dioxo moiety(compound 26) or a hydrogen atom (compound 2). The compounds disclosed by D6 are alpha-1-adrenergic receptor blockers, useful to treat the same diseases as in the present case.

D5 disclose alpha-1-adrenergic receptor blockers, which present an isolated or condensate pyrrolidin-2,5-dione moiety linked through an alkylene moiety through a 1,4-disubstituted piperazine. Moreover the R substituent of D5 can also be an alkyl moiety as in the present case for R1.

Since D1 discloses compounds with the same activity as the present ones and moreover they are novelty-destroying embodiments for the subject-matter claimed by the present Claims 1, 10, 11, and on the other hand from the D6 and D5 seems that the presence of the piperazine and 2-5-dioxopyrrolidine ring are important for the claimed activity (and not the nature of the R1 substituent) no inventive step can be acknowledged for the subject-matter of the present Claim 2-5, 12-36 since it is not yet shown by appropriate information, e.g. in form of experimental data, that substantially all the claimed compounds have an unexpected property or improved activity over the structurally closest prior art compounds (D1 and D6), which is attributable to the distinguishing feature of the invention.

5. **Industrial applicability** (Article 33(4)PCT).

For the assessment of the present claims 39-48 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO,

for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.